(3) *pH.* Proceed as directed in § 436.202 of this chapter, using an aqueous solution containing 100 milligrams of cefuroxime per milliliter.

(4) *Identity.* Proceed as directed in § 442.18a(b)(6).

[54 FR 40654, Oct. 3, 1989; 54 FR 50686, Dec. 8, 1989]

§ 442.18a Sterile cefuroxime sodium.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Cefuroxime sodium is the sodium salt of (6*R*, 7*R*)-3-carbamoyloxy-methyl-7-[(2*Z*)-2-(2-furyl)-2-methoxyiminoacetamido] cepha-3-em-4-carboxylic acid. It is so purified and dried that:

(i) If the cefuroxime is not packaged for dispensing, its cefuroxime content is not less than 855 micrograms and not more than 1,000 micrograms of cefuroxime per milligram on an anhydrous basis. If the cefuroxime is packaged for dispensing, its cefuroxime content is not less than 855 micrograms and not more than 1,000 micrograms of cefuroxime per milligram on an anhydrous basis and also, each container contains not less than 90 percent and not more than 120 percent of the number of milligrams of cefuroxime that it is represented to contain.

(ii) It is sterile.

(iii) It is nonpyrogenic.

(iv) Its moisture content is not more than 3.5 percent.

(v) Its pH in an aqueous solution is not less than 6.0 and not more than 8.5.

(vi) It gives a positive identity test.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for cefuroxime content, sterility, pyrogens, moisture, pH, and identity.

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research:

(*a*) If the batch is packaged for repacking or for use as an ingredient in the manufacture of another drug:

(*1*) For all tests except sterility: 10 packages, each containing approximately 1 gram.

(*2*) For sterility testing: 20 packages, each containing approximately 1 gram.

(*b*) If the batch is packaged for dispensing:

(*1*) For all tests except sterility: A minimum of 10 immediate containers.

(*2*) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) *Tests and methods of assay*—(1) *Cefuroxime content.* Proceed as directed in § 436.343 of this chapter.

(2) *Sterility.* Proceed as directed in § 436.20 of this chapter, using the method described in paragraph (e)(1) of that section.

(3) *Pyrogens.* Proceed as directed in § 436.32(b) of this chapter, using a solution containing 50 milligrams of cefuroxime per milliliter.

(4) *Moisture.* Proceed as directed in § 436.201 of this chapter, using the titration procedure described in paragraph (e)(1) of that section.

(5) *pH.* Proceed as directed in § 436.202 of this chapter, using an aqueous solution containing 100 milligrams per milliliter.

(6) *Identity.* From the high-pressure liquid chromatograms of the sample and the cefuroxime working standard determined as directed in paragraph (b)(1) of this section, calculate the adjusted retention times of the cefuroxime in the sample and standard solutions as follows:

$$\text{Adjusted retention time of cefuroxime} = t - t_a$$

where:

t = Retention time measured from point of injection into the chromatograph until the maximum of the cefuroxime sample or working standard peak appears on the chromatogram; and

t_a = Retention time measured from point of injection into the chromatograph until the maximum of nonretarded solute appears in the chromatogram.

The sample and the cefuroxime working standard should have corresponding adjusted cefuroxime retention times.

[48 FR 38461, Aug. 24, 1983, as amended at 55 FR 11583, Mar. 29, 1990]

§ 442.19 Cefuroxime axetil.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Cefuroxime axetil is an amorphous mixture of the diastereoisomers of 5-thia-1-azabicyclo[4.2.0]oct-

2-ene-2-carboxylic acid, 3-[[(aminocarbonyl)oxy]methyl]-7-[[2-furanyl(methoxyimino)acetyl]amino]-8-oxo-, 1-(acetyloxy)ethyl ester, [6*R*-[6 *alpha*, 7 *beta* (*Z*)]]-. It is so purified and dried that:

(i) Its potency is not less than 745 micrograms and not more than 875 micrograms of cefuroxime per milligram on an anhydrous basis. The ratio of isomer A to total isomer content is not less than 0.48 and not more than 0.55.

(ii) Its moisture content is not more than 1.5 percent.

(iii) It is amorphous and not crystalline.

(iv) It passes the identity test.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Request for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for cefuroxime potency, isomer A ratio, moisture, crystallinity, and identity.

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research: 10 packages, each containing approximately 500 milligrams.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in § 436.216 of this chapter, using ambient temperature, an ultraviolet detection system operating at a wavelength of 278 nanometers, a 25-centimeter by 4.6-millimeter column packed with methyl silane bonded silica 5 micrometers in particle size, a flow rate of 1 milliliter per minute, and a known injection volume of 10 microliters. Reagents, working standard and sample solutions, system suitability requirements, and calculations are as follows:

(i) *Reagents*—(A) *0.2M Ammonium phosphate solution.* Transfer 23.0 grams of ammonium dihydrogen phosphate to a 1-liter volumetric flask. Dissolve and dilute to volume with distilled water. Mix well.

(B) *Mobile phase.* Transfer 380 milliliters of methanol to a 1-liter volumetric flask and dilute to volume with 0.2*M* ammonium phosphate solution.

(C) *Internal standard solution.* Prepare a solution containing 5.4 milligrams of acetanilide per milliliter in methanol.

(D) *System suitability test solution.* Mix 10.0 milliliters of a solution containing 1.2 milligrams of cefuroxime axetil working standard per milliliter in methanol with 5.0 milliliters of internal standard solution, 2.0 milliliters of a solution containing 0.3 milligram of an authentic sample of (*RS*)-1-acetoxyethyl (6*R*, 7*R*)-3-carbamoyloxymethyl-7-[(2′*Z*)-2-(fur-2-yl)-2-methoxy-iminoacetamido]ceph-2-em-4-carboxylate (delta-2 isomers of cefuroxime axetil) per milliliter in methanol and 1.8 milliliters of methanol. Dilute to 50 milliliters with 0.2*M* ammonium phosphate solution.

(ii) *Preparation of working standard and sample solutions*—(A) *Working standard solution.* Dissolve approximately 30 milligrams of the cefuroxime axetil working standard, accurately weighed, in methanol and dilute to 25 milliliters with methanol. Immediately transfer 10.0 milliliters of the working standard solution to a 50-milliliter volumetric flask. Add 5.0 milliliters of internal standard solution and 3.8 milliliters of methanol, and dilute to volume with 0.2*M* ammonium phosphate soluton to obtain a solution containing 0.2 milligram of cefuroxime activity per milliliter. Store the solution under refrigeration no more than 8 hours.

(B) *Sample solution.* Dissolve approximately 30 milligrams of the sample, accurately weighed, in methanol and dilute to 25 milliliters with methanol. Immediately transfer 10.0 milliliters of the sample solution to a 50-milliliter volumetric flask. Add 5.0 milliliters of internal standard solution and 3.8 milliliters of methanol, and dilute to volume with 0.2*M* ammonium phosphate solution to obtain a solution containing 0.2 milligram of cefuroxime activity per milliliter (estimated). Store the solution under refrigeration no more than 8 hours.

(iii) *System suitability requirements*—(A) *Tailing factor.* The tailing factor (*T*) is satisfactory for isomer A if it is not more than 1.5 at 5 percent of peak height.

(B) *Efficiency of the column.* The efficiency of the column (*n*) is satisfactory

for isomer A if it is greater than 3,000 theoretical plates.

(C) *Resolution.* The resolution (*R*) between isomer A and isomer B of cefuroxime axetil is satisfactory if it is not less than 1.5 and the resolution (*R*) between isomer A and the delta-2 isomers of cefuroxime axetil is satisfactory if it is not less than 1.5.

(D) *Coefficent of variation.* The coefficient of variation (S_R in percent) of five replicate injections is satisfactory if it is not more than 2.0 percent. If the system suitability requirements have been met, then proceed as described in § 436.216(b) of this chapter. Alternate chromatographic conditions are acceptable provided reproducibility and resolutiona recomparable to the system. However, the sample preparation described in paragraph (b)(1)(ii)(B) of this section should not be changed.

(iv) *Calculations*—(A) Calculate the micrograms of cefuroxime per milligram of sample as follows:

$$\text{Micrograms of cefuroxime per milligram} = \frac{R_u \times P_s \times 100}{R_s \times C_u \times (100 - m)}$$

where:

R_u = Sum of the peak height of the cefuroxime axetil sample isomer A and isomer B peaks/Peak height of the internal standard;

R_s = Sum of the peak heights of the cefuroxime axetil working standard isomer A and isomer B peaks/Peak height of the internal standard;

P_s = Cefuroxime activity in the cefuroxime axetil working standard solution in micrograms per milliliter;

C_u = Milligrams of sample per milliliter of sample solution; and

m = Percent moisture content of the sample.

(B) Calculate the ratio of isomer A to total isomer content as follows:

$$\text{Ratio of isomer A to isomer content} = \frac{\text{Peak height of isomer A peak}}{\text{Peak height of isomer A peak} + \text{Peak height of isomer B peak}}$$

(2) *Moisture.* Proceed as directed in § 436.201 of this chapter, using the titration procedure described in paragraph (e)(1) of that section.

(3) *Crystallinity.* Proceed as directed in § 436.203(a) of this chapter, except that the particles do not reveal the phenomena of birefringence and extinction positions on revolving the microscope stage.

(4) *Identity.* Proceed as directed in § 436.211 of this chapter, using the mineral oil mull prepared as described in paragraph (b)(2) of that section.

[52 FR 42432, Nov. 5, 1987; 52 FR 43966, Nov. 17, 1987; 52 FR 45528, Nov. 30, 1987, as amended at 54 FR 47351, Nov. 14, 1989; 55 FR 11583, Mar. 29, 1990]

§ 442.20a Sterile cefonicid sodium.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Sterile cefonicid sodium is a white to off-white lyophilized powder. It is so purified and dried that:

(i) If the cefonicid sodium is not packaged for dispensing, its cefonicid content is not less than 832 micrograms and not more than 970 micrograms of cefonicid per milligram on an anhydrous basis. If the cefonicid sodium is packaged for dispensing, its cefonicid content is not less than 832 micrograms and not more than 970 micrograms of cefonicid per milligram on an anhydrous basis and also, each container contains not less than 90 percent and not more than 120 percent of the number of milligrams of cefonicid that it is represented to contain.

(ii) It is sterile.

(iii) It is nonpyrogenic.

(iv) Its moisture content is not more than 5.0 percent.

(v) Its pH in an aqueous solution containing 50 milligrams per milliliter is not less than 3.5 and not more than 6.5.

(vi) The specific rotation in a methanol solution containing 10 milligrams of cefonicid sodium per milliliter at 25° C is −42°±5°.

(vii) It passes the identity test.